Chapter 1

General Introduction

1.1 Nutraceuticals

The term nutraceutical is a portmanteau word derived from nutrition and pharmaceutical. The term is coined in 1989 by Stephen L. De Felice, Founder and Chairman, The Foundation for Innovation in Medicine, Cranford,New Jersey. Nutraceuticals, in general, refer to isolated nutrients, dietary supplements, genetically engineered "designer" food, herbal products, and processed products like cereals, soups, and beverages[1]. A nutraceutical is any nontoxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease[2]. However, according to Dr. Lockwood, the nutraceutical is defined as "a medicinal or nutritional component that includes a food, plant or naturally occurring material which may have been purified or concentrated and that is used for the improvement of health, by preventing or treating a disease[3]". Whereas, Health Canada defines nutraceutical as "a product prepared from foods, but sold in the form of pills, or powder (potions) or in other medicinal forms, not usually associated with foods"[4]. Vitamin E, selenium, vitamin D, green tea, soy, and lycopene are examples of nutraceuticals.

The pharmaceutical value of foods is well-recognized as far back as in the time of Hippocrates (400 BC) who observed "Let food be thy medicine and medicine be thy food "Indian, Egyptian, Chinese and Sumerian civilizations provide evidence to the therapeutic values of foods. The Ayurveda, the 5000 year old health science of India, has mentioned the benefits of food for therapeutic purposes .The nutraceuticals are not drugs, which are powerful pharmacologically active substances that will increase, decrease or otherwise modify any physiological or metabolic function[5]. Nutraceuticals also refer to natural functional/medical foods or bioactive phytochemicals that have health-promoting, disease-

preventing or medicinal properties. Depending on their emphases, these nutraceuticals generally contain vitamins, lipids, proteins, minerals etc. Based upon their chemical structures and biological functions, these nutraceuticals are used in nutritional therapy. When a dietary supplement, nutraceutical or other feed is planned to be used for the treatment or prevention of disease, in reality, it becomes a drug. In fact, they are an emerging class of natural products that makes the difference between foods and drugs to vanish[6].

There has been change in human lifestyles over the last few decades due to the rapid industrialization and changing work cultures which have led people to various fast-food eating cultures, but this has decreased the quantity and quality of nutrients. At the same time, industrialization has concurrently brought forth air and water pollution, and soil and food contamination because of extensive use of various chemicals, electromagnetic waves, and other potentially harmful man-made items. These problems have led to an increased incidence of diabetes, obesity, cancers, vascular diseases, physiological problems, as well as other degenerative diseases leading to severe immune dysfunction[7].

The consumers are acutely bothered about how their health care is managed, administered and taxed. They are frustrated with the expensive, high-tech, disease-treatment and management approach predominant in modern medicine; as the consumer is seeking complementary or alternative beneficial products and the advent of nutraceuticals is tempting. In maintaining normal function of the human body , a vital role is played by adequate nutrients obtained from various foods .With the recent advances in medical and nutrition sciences, natural products and health-promoting foods have received extensive attention from both the health professionals and the man in general. New concepts have

appeared with this trend, such as nutraceuticals, nutritional therapy, phytonutrients, and phytotherapy[8]. The nutraceuticals are found in a variety of products coming out from (a) the food industry, (b) the herbal and dietary supplement market, (c) pharmaceutical industry. The goal of achieving an optimal or maximal state of nutrition and health is becoming an increasing challenge with the introduction of many nutraceuticals[9]. Although most nutraceuticals currently used are known as vital nutrients for the human body, many details such as dose, drug-drug interaction, nutraceutical-drug interaction, and their effects on individuals under certain health conditions remain shrouded in mystery[10].

There is utmost scientific challenge regarding the standardization of the nutraceutical compounds and carefully develop and execute clinical studies to provide the basis for health claims to produce an impact on the consumers and also on the nutraceutical companies. The response of nutraceuticals varies from person to person. Individual's susceptibility to any particular disease depends on the genetic predisposition, environmental factors and lifestyle. But the role of nutraceuticals in the prevention, restriction and the cure of various diseases is beyond question.

The presence of secondary metabolites in plants is known to wield a wide range of biological activities and therefore some plant-derived foods have the ability to reduce the risk of chronic diseases. In general, these metabolites have low potency as bioactive compounds when compared to drugs, but since they are ingested on a regular basis and in large amounts as part of the diet, they may have a noticeable long-term physiological effect[11]. There are various biological mechanisms by which the nutraceuticals exert positive influences on the patho-physiological processes .These products are safe and well tolerated, but the interpretation of collective results is hampered by the heterogeneity of

studies, inconsistent results, and not well designed investigations. On the other hand, nutraceuticals are expected to be substantially safer and with less secondary effects than many drugs routinely prescribed for the treatment of certain symptoms; however, they are often expensive, lack pharmaceutical-level manufacturing standard controls, and may not work[12]. An additional problem regarding the production and consumption of nutraceuticals is that the composition and the contents of active constituents in natural plants vary depending on season, climate, temperature, humidity, soil etc. So the collection, identification and maintenance of uniform quality, quantification and standardization are the critical factors to be considered.

With the economic development, there has been considerable improvement of lifestyle. But this improvement has brought about the menace of lifestyle diseases which is due to weird food habits. The widespread use of junk food leads to a number of diseases allied to nutritional deficiencies. The therapeutic value of nutraceuticals in controlling these diseases is worthy to be noted. Keeping pace with the time, more people are turning towards nutraceuticals. Plant biotechnologists have put forth incalculable efforts to engineer plants and crops in a bid to improve their nutritional value for better health. It has also been proved that any excess intake of any nutrient may not benefit or even can be fatal to human health. Already there are many plant biotechnological products currently, which are patented for their medicinal values. The products marketed as functional foods and nutraceuticals are highly variable and are often dependent upon historical if not local allegiances. The nutraceuticals are marketed in concentrated forms as pills, capsules, powders and tinctures either as a single substance or as combined preparations. The functional food and nutraceutical products embody a value-added growth opportunity for

the agri-food industry, both domestically as well as internationally. The market is driven by the aging population, rising health care costs, advances in food technology and nutrition, as well as a growing consumer consciousness of the link between diet and health. The scientific studies have also expanded to these areas and have given support to many of these products and therapeutic services. Most of the immune mediators like lack of physical exercise, poor diet, negative emotions and environmental toxicity along with the progression of age, cause variable effects on the human system[12].

Because of media hype, the increasing awareness levels about fitness and health are turning the majority of people to lead healthier lifestyles, exercise more, and eat healthy. The expanding nutraceutical market indicates that the users are seeking minimally processed food with extra nutritional benefits and organoleptic value. This development, in turn, is propelling expansion in the nutraceutical markets globally. The emerging nutraceuticals industry seems destined to occupy the landscape in the new millennium. Its tremendous growth has implications for the food, pharmaceutical, healthcare, and agricultural industries. Like drugs, there should be strict regulatory controls over nutraceuticals.

1.2 Uses of Nutraceuticals:

The oxidative stress plays a vital role in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Oxidative stress is accelerated by the ageing process along with the lack of dietary antioxidants. The studies have shown that there is an association between high dietary antioxidant intake and a decreased risk of AD[14] . Nutraceutical antioxidants such as curcumin, lutein, lycopene, turmerin and β-carotene may exert positive effects on specific

diseases by working against oxidative stress. It is noted in this connection that alpha-lipoic acid and phosphatidylserine are promising nutraceuticals for early dementia, early AD, and age-related cognitive disorders.

The cardiovascular disease (CVD) is the major cause of deaths in the developing nations. The CVD[15] patients are advised to take more fruits and vegetables as nutraceuticals. The dietary intake in the form of fibres, omega-3 polyunsaturated fatty acids (n-3 PUFAs), vitamins, minerals together with physical exercise are recommended for CVD patients. It has been shown that the molecules like polyphenols present in grapes and in wine alter cellular metabolism and signaling, which is consistent with reducing arterial diseases .The Flavonoids (found in grapes, berries, onions etc.) are widely distributed in plants and play a major role in preventing and curing CVDs. The flavonoid intake was significantly inversely associated with mortality from coronary heart disease and the incidence of myocardial infarction. The phytosterols[16] compete with dietary cholesterol by blocking the uptake as well as facilitating its excretion from the body. Hence, they have the power to reduce the morbidity and mortality of CVD patients.

The obesity is globally prevalent irrespective of age and socio-economic status. The optimum nutrition and regular exercise are recommended. However, nutraceuticals such as conjugated linoleic acid, capsaicin, Mimordia charantia, chitosan, fenugreek, are known to reduce obesity[17]. It is noted that herbal agents, such as caffeine, ephedrine, chitosan and green tea are effective in reducing body weight.

Cancer is a major global health concern. The carotinoids are a group of phytochemicals with antioxidant activities are effective for cancer prevention. Plants rich in daidzein, biochanin, isoflavones, lycopene and genistein also inhibit prostate cancer cell growth[18]. β-

carotene has antioxidant activity and prevents cancer and other diseases. The citrus fruit flavonoids, soya food isoflavones and curcumin from curry have chemopreventive properties. Saponins and tannins are reported to have antimutagenic and antitumor activities and may lower the risk of human cancers, by preventing cancer cells from growing. Lipoic acid is an antioxidant used for the treatment of diabetic neuropathy. It is possible that lipoic acid may be more effective as a long-term dietary supplement aimed at the prophylactic protection of diabetics from complications. Dietary fibers from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight reduction, for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia[19,20]. The extracts of bitter melon and cinnamon show the potential to treat and possibly prevent diabetes.

The herbs or herbal extracts, such as green tea, *Allium* spp., Vitamins C and E, polyphenols, carotenoids (mainly lycopene and β-carotene), and coenzyme Q10 have antioxidant properties and effective in age-related macular degeneration (AMD)[21]. Astaxanthin offers powerful protection for the eyes and prevents macular degeneration. Lutein and Zeaxanthin are used for the treatment of visual disorders. A number of nutraceuticals have been shown to play crucial role in immune status and susceptibility to some disease conditions. Osteoarthritis is a debilitating joint disorder which affects a large number of population. Glucosamine and chondroitin sulfate are widely used for the alleviation of symptoms of osteoarthritis. Nutraceuticals like ginger, soybean, glucosamine, chondroitin, S-adenosylmethionine give relief from the symptoms of osteoarthritis. The herbal nutraceuticals with anti-inflammatory activity are also available and Gentianine, present in Gentian root, is an effective anti-inflammatory agent.

The antiangiogenic compounds are selective against newly formed blood vessels while sparing existing ones may not lead to side effects even after prolonged exposure. Such compounds may prevent diseases involving degenerative process such as multiple sclerosis, arthritis, osteoporosis, diabetes, cancer, AD and Parkinson's diseases. Some bioactive compounds such as curcumin, flavins, isoflavones and catechins, resveratrol, proanthocyanidins, flavonoids, Saponins, terpenes, Chitin, chitosan, Vitamins B3 and D3, Fatty acids, peptides and amino acids are potentially effective angiogenic compounds[22].

1.3 Metal nanoparticles:

The prefix nano - is derived from the Greek word nannus, meaning dwarf. It was adopted as an official SI prefix, meaning 10^{-9}. Nanoparticles are nanosized structures in which at least one of its phases has one or more dimensions (length, width or thickness) in the nanometer size range (1 to 100 nm). Historically, the existence of metallic nanoparticles in solution was first recognized by Faraday in 1857 and however, Mie gave a quantitative explanation of their colour in 1908. In general, the size of a nanoparticle spans the range between 1 and 100 nm. Metallic nanoparticles (MNPs) have different physical and chemical properties from bulk metals (e.g., lower melting points, higher specific surface areas, specific optical properties, mechanical strengths, and specific magnetizations), properties that are helpful in various industrial applications. However, how a nanoparticle is viewed and is defined depends very much on the specific application. For his outstanding work in the field of modern colloid chemistry by studying the properties of gold sols and inventing an ultra microscope, Richard Zsigmondy got the Nobel Prize in chemistry in 1925. But the industrial production of nanomaterials has started in the twentieth century. For example, nanoparticles of carbon black (tire soot) have been used in

the fabrication of rubber tires of automobiles from the beginning of the twentieth century. The pigments such as SiO_2 and TiO_2 have been prepared by a high-temperature combustion method. Since the 1970s, the innovative development of nanoparticles is due to a combination of theory and experiments in the fields of physics, chemistry, materials science, and biosciences.

There are two methods for the synthesis of MNPs. The first method is the breakdown (top-down) method by which an external force is applied to a solid that leads to its break-up into ultrathin particles. The second method is the build-up (bottom-up) method that produces MNPs starting from atoms of gas or liquids based on atomic transformations or molecular condensations. However, the synthesis of MNPs should fulfill the conditions, such as (1) control of particle size, size distribution, shape, crystal structure and composition distribution, (2) improvement of the purity of nanoparticles (lower impurities), (3) control of aggregation, (4) stabilization of physical properties, structures and reactants, (5) higher reproducibility. To add further, two main colloidal methods are broadly employed for the preparation of MNPs: (co or nano) precipitation and chemical reduction. In some cases, the presence of surfactant (capping agent) is required to control the particle nucleation, growth, and stability. Typically, the co-precipitation reactions involve the thermal decomposition of organometallic precursors and the precipitation of new reaction materials or compounds[23]. The chemical reduction occurring in colloidal assemblies is another approach for the formation of size- and shape-controlled nanoparticles.[24] The colloids of gold nanoparticles are one of the most stable and easiest to handle .The general synthetic procedure to prepare nearly mono-disperse gold colloids involves the reduction of metal salts in the presence of surfactants and then stabilizing the

particles with a capping ligands present in the solution[25]. In general, particle size and size distribution play a significant role in controlling the properties of any colloid based upon a nanomaterial.[26]

The formation of nanoparticles using plant extracts has more advantage over other methods in terms of its interaction and effect on the environment; it is completely environmental friendly and does not pose any threats even from its waste. The time required for the formation of particles is also within the acceptable limits and with the ease of getting the requisite plants make it one of the best methods available in this field to develop the particles. The plant extracts containing bioactive alkaloids, phenolic acids, polyphenols, proteins, sugars, and terpenoids are believed to have an important role in first reducing the metallic ions and then stabilizing them. The variation in composition and concentration of these active bio-molecules between different plants and their subsequent interaction with aqueous metal ions is believed to be the main contributing factors to the diversity of nanoparticle sizes and shapes produced[27]. The synthesis of nanoparticles from reducing metal salts via plants is a relatively easy room temperature process. The process begins by mixing a sample of plant extract with a metal salt solution. Biochemical reduction of the salts starts immediately and the formation of nanoparticles is indicated by a change in the colour of the reaction mixture. During the synthesis, there is an initial activation period when process metal ions are converted from their higher oxidation states to zero-valent states and nucleation of the reduced metal atoms takes place[28]. This is immediately followed by a period of growth when smaller neighboring particles combine to form larger nanoparticles that are thermodynamically more stable while further biological reduction of metal ions takes place. As a growth of progresses nanoparticles

aggregate to form a variety of morphologies. In the final stage of synthesis, the plant extracts' ability to stabilize the nanoparticle ultimately determines it's most energetically favourable and stable morphology. The properties of the plants extract such as its concentration, metal salt concentration, reaction time, reaction solution pH, and temperature significantly influence the quality, size, and morphology of the synthesized nanoparticles[29].

During the biological synthesis of metallic nanoparticles, a number of controlling factors are involved in the nucleation and subsequent formation of stabilised nanoparticles. These factors include pH, reactant concentrations, reaction time, and temperature. Studies have shown that varying the pH of the reaction medium tends to produce variability in shape and size of nanoparticles synthesized. In particular, larger particles tend to be produced at a lower acidic pH values.

1.4 Uses of metal nanoparticles :

MNPs can be used in myriads of fields from materials science, engineering right up to bioscience, biotechnology etc. The large surface area per unit volume, special opto-electronic and magnetic properties make their versatility in use in plethora of applications. Carbon nano particles are used to develop low cost electrodes of fuel cells replacing valuable Platinum electrodes. Based on the impact of sunlight on concentrated nanoparticles thereby producing steam with high energy efficiency, a solar steam system has been devised which is used for the purification of water and the disinfection of dental appliances. As catalyst, metallic nano particles are selective, highly reactive and have long life time. Both heterogeneous and homogeneous catalysis are possible. Examples are oxidation reaction, olefin hydrogenation reaction. Whereas, Ni, Pd, Ag and Pt have been

used as typical metal catalysts in chemical reactions. However, the dissociative adsorption of hydrogen or oxygen molecules cannot be carried out on an Au smooth surface and at a temperature[30] of less than 200 °C. Therefore, such a gold material is inactive as a catalyst in hydrogenation and oxidation reactions. However, when Au nanoparticles are used, they work effectively as catalysts[31]. Metal nanoparticle paste is used for circuit pattern formation of a printed wired board in the electronic industry[32]. When polymers are filled with nanotubes, their mechanical properties are improved. Such improvement is also observed when nano particles are mixed with metals or ceramics. Because of photo-catalytic activity and UV protection, nano TiO_2 is used in paints. However, the paint gives better micro hardness, scratch resistance upon addition of nano SiO_2 . The real bone is a nano-composite material, composed of hydroxyl-apatite crystallites in an organic matrix composed of collagen. The bone is mechanically tough and plastic, such that it can recover from a mechanical damage. Based on the fact that natural bone surface is quite often contains features that are about 100 nm across, artificial prosthetic limbs have been developed using metal nano particles. Metal nano particles are also used in sunscreen lotion as they cut off UV rays aptly for prolonged exposure. MNPs are also used in drug delivery and polymeric micelle nanoparticles are used to deliver drugs to tumor cells.The polymer coated iron oxide nanoparticles and silver nanoparticles are used for the treatment of chronic bacterial infections. The nanodiamonds with chemotherapy drugs attached to them are used to treat brain tumor and leukaemia. The synthetic skin is developed with a composite of nickel nanoparticle and polymer.

1.5 References :

1. DeFelice S. L. Nutraceuticals: Opportunities in an Emerging Market. Scrip Mag : 1992; 9.

2. Dillard, C. J., German, J. B. J Sci Food Agric : 2000; 80:1744-1756.

3. Lockwood, B. Nutraceuticals, 2nd Edition. London, UK: Pharmaceutical Press, 2007 , pp. 1.

4. Wildman R.E.C., editor. Handbook of nutraceuticals and functional foods . Boca Raton : CRC Press ; 2001 , pp. 13-30 .

5. Doyon M, Labrecque J. British Food Journal : 2008; 110(11):1133-1149.

6. Adelaja A.O, Schilling B.J. Mag. Food Farm Resour. Issues : 1999 ; 14 : 35-40 .

7. Lakshmana Prabu et al. International Journal of Health and allied sciences : 2012 ; 1(2) : 47-53 .

8. Bland J.S. Altern. Ther. Health Med. : 1996 ; 2 : 73-76 .

9. Gibson R.A , Makrides M. Am. J. Clin. Nut. : 2000 ; 71 : 251-255 .

10. Mobarhan S. Nutr. Rev. : 1994 ; 52 : 102-105 .

11. Espín J. C, García-Conesa M.T., Tomás-Barberán F.A. Phytochemistry : 2007 ; 68 : 2986-3008.

12. McAlindon T.E. Nutraceuticals: Clin. Rheumatol. : 2006 ; 20 : 99-115.

13. Rani et al. World Journal of Pharmaceutical Research : 2016 ; 5(7) : 452-468 .

14. Klatte E.T, Scharre D.W, Nagaraja H.N, Davis R.A, Beversdorf D.Q. Alzheimer Dis Assoc Disord : 2003; 17: 113-116.

15. Hu F.B and Willett W.C. JAMA : 2002 ; 288 : 2569-2578 .

16. Gita C. Curr Top Nutraceutical Res.: 2004; 2: 113–21.

17. Kasbia G.S. Nutr Food Sci. : 2005;35: 344- 51.

18. Kruger C.L, Murphy M, DeFreitas Z, Pfannkuch F, Heimbach J. Food Chem Toxicol. : 2002; 40: 1535–1549.

19. Coleman M.D, Eason R.C and Bailey C.J. Environmental Toxicology and Pharmacology: 2001; 10: 167-172.

20. Baljit S. Int.J.Pharmaceutics: 2007;334: 1-14.

21. Brouns F. Food Res Int.: 2002; 35: 187–193.

22. Baradaran A, Madihi Y, Merrikhi A, Rafieian-Kopaei M, Nematbakhsh M, Asgari A, et al. Pak J Med Sci.: 2013; 29: 329–333.

23. Dumestre F, Chaudret B, Amiens C, Fromen M.C, Casanove M.J, Renaud P, Zurcher P. Angew Chem : 2002 ; 114:4462–4465 .

24. Pileni M.P. Nat Mater : 2003 ; 2:145–150 .

25. Brust M, Walker M, Bethell D, Schiffrin D.J, Whyman R. J Chem Soc, Chem Commun : 1994 ; 801–802 .

26. Xiong Y, Chen J, Wiley B, Xia Y, Aloni S, Yin Y. J Am Chem Soc : 2005 ;127:7332–7333 .

27. Li, X.; Xu, H.; Chen, Z.S.; Chen, G. J. Nanomater.: 2011; 2011: 270974.

28. Malik, P.; Shankar, R.; Malik, V.; Sharma, N.; Mukherjee, T.K. J. Nanopart.: 2014; 2014: 302429.

29. Dwivedi, A.D.; Gopal, K. Colloids Surf. A : 2010; 369: 27–33.

30. Saliba , N. , Parker , D.H. , and Koel , B.E. Surf. Sci. : 1998 ; 410 : 270 – 282 .

31. Haruta , M. Chem. Rec.: 2003 ; 3 : 75 – 87 .

32. Kawazome , M. , Kim , K. , Hatamura , M. , and Suganuma , K. Funsai , : 2006 ; 50 : 27 – 31 .